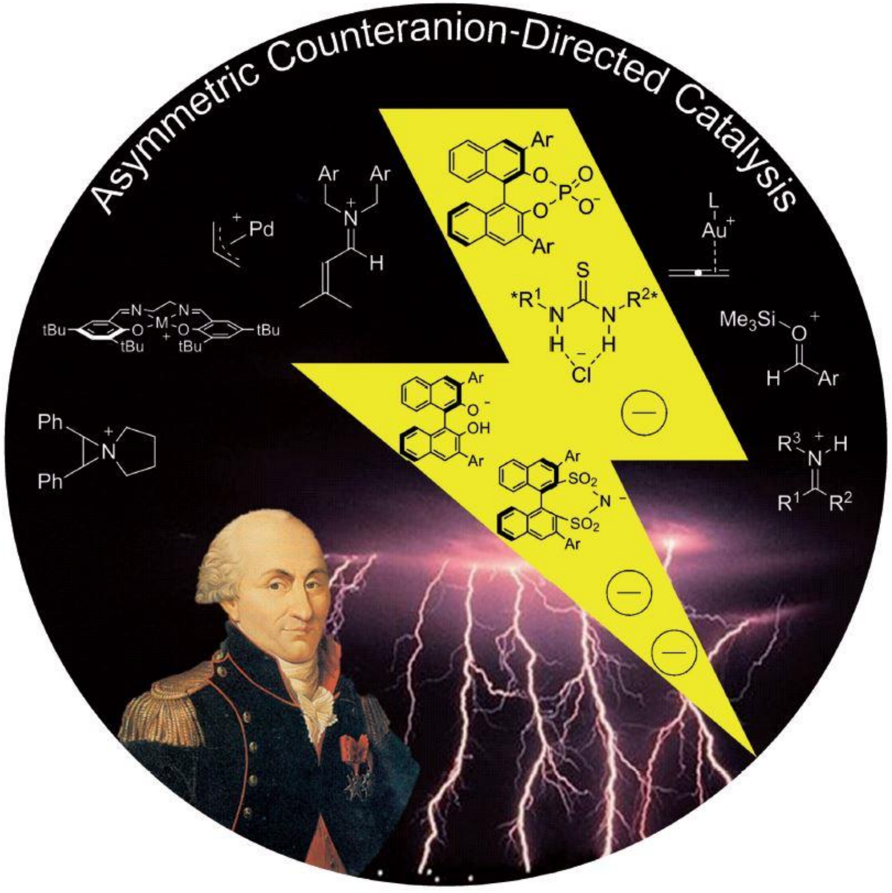
Asymmetric Counteranion-Directed Catalysis in Organocatalysis



Reporter: Fengjin Wu

Supervisor: *Prof*. Huang

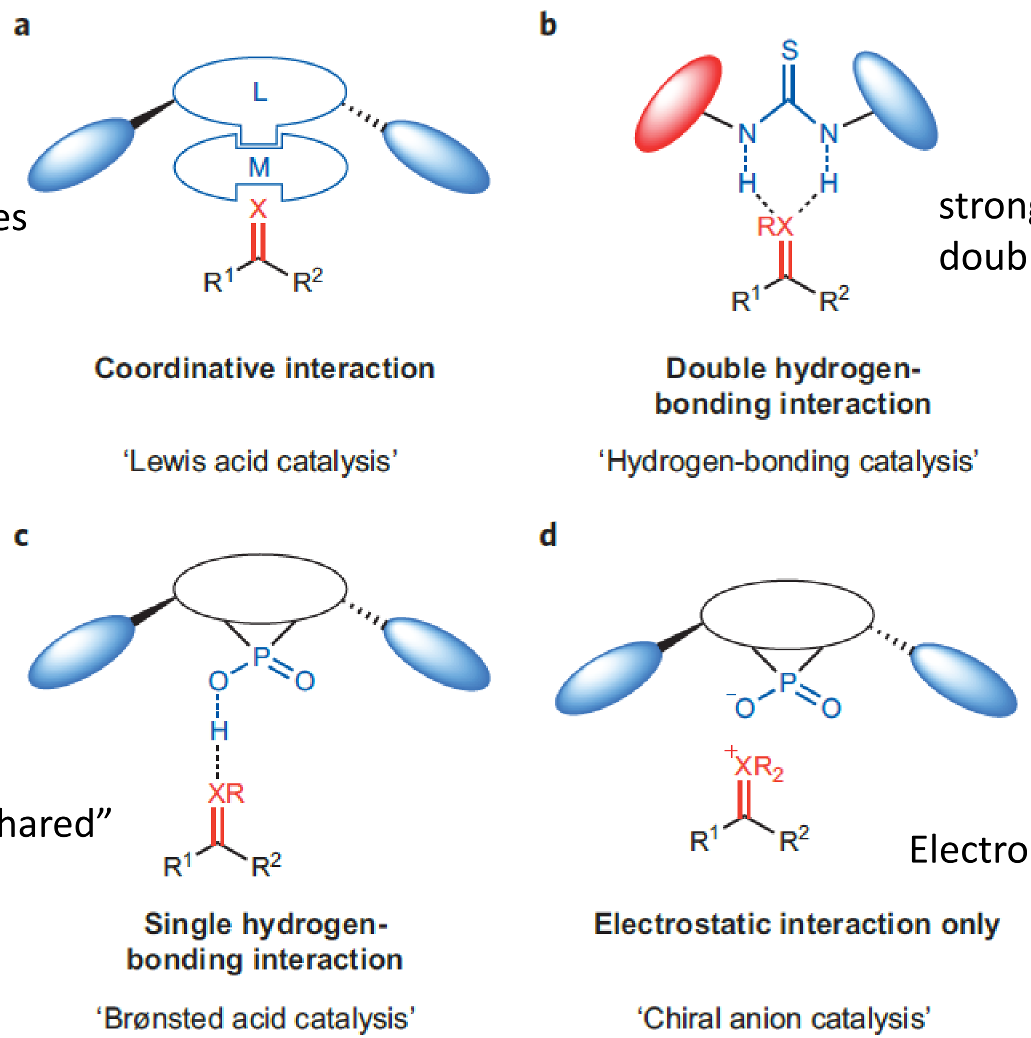
Date: 03. 11. 2019

Outline:

1. Introduction
2. Applications in organocatalysis
    2.1. Chiral counterions in Brønsted acid catalysis
    2.2. Chiral counterions in Lewis acid catalysis
    2.3. Chiral counterions combining with amine
    2.4. Chiral anion binding from hydrogen-bonding catalysts
    2.5. Chiral counterions in phase-transfer catalysis
3. Conclusion
4. Acknowledgement

1. Introduction

Representative asymmetric activation modes:



Lewis acidic metal combines with a chiral basic ligand

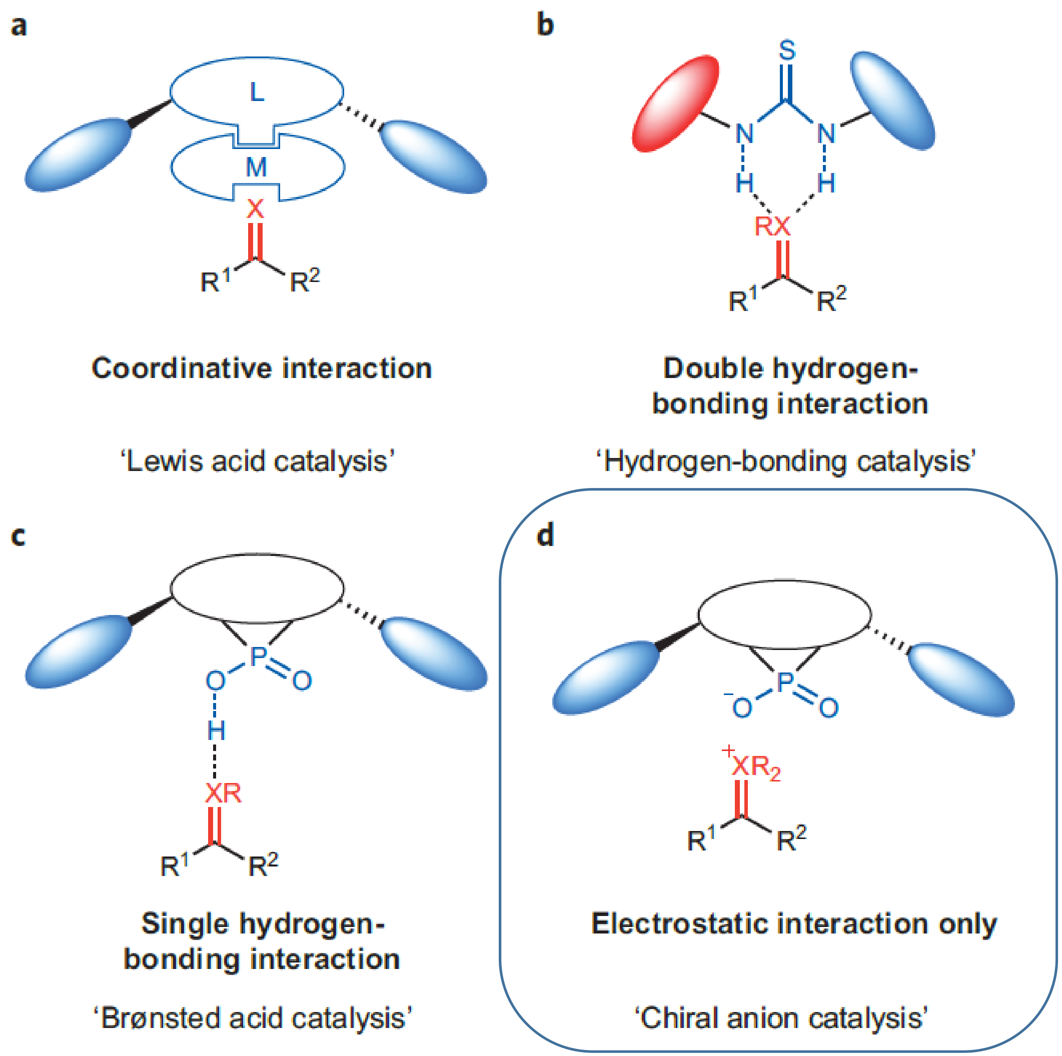
strong and directional double hydrogen bonds

the proton is effectively "shared"
Bifounctional catalysis

Electrophile was protonated.

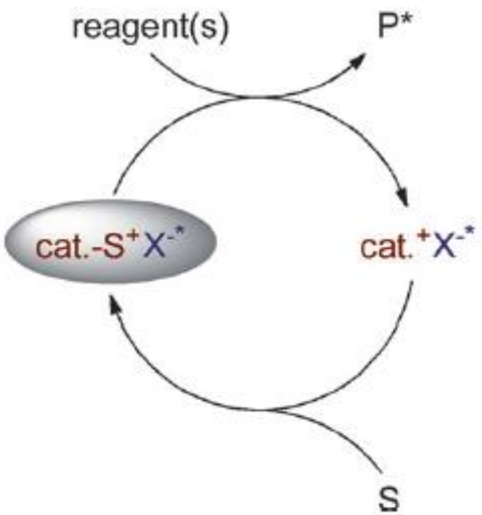
1. Introduction

Representative asymmetric activation modes:



1. Introduction

What is Asymmetric Counteranion-Directed Catalysis (ACDC) :



Asymmetric counteranion-directed catalysis refers to the induction of enantioselectivity in a reaction proceeding through a cationic intermediate by means of ion pairing with **a chiral, enantiomerically pure anion** provided by the catalyst.

Stablizing interactions in ion-pairs:

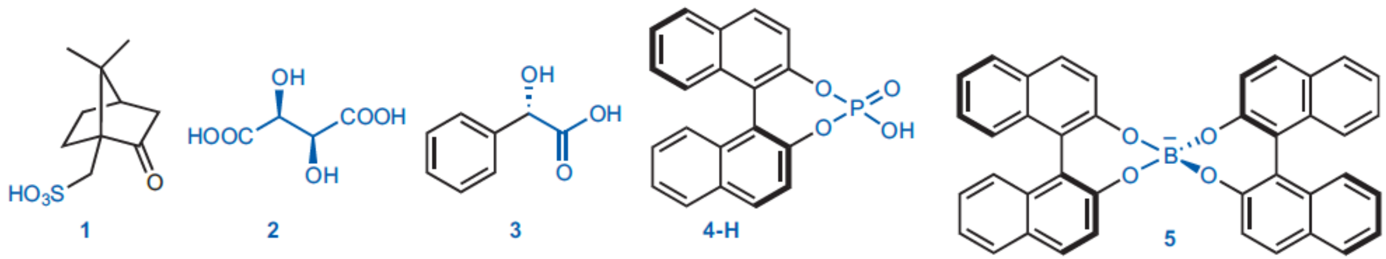
1. Coulombic attraction;
2. Hydrogen bonding interaction;
3. Even covalent bonding (not in enantiodeterming step)

Angew. Chem. Int. Ed. **2013**, 52, 518 – 533.

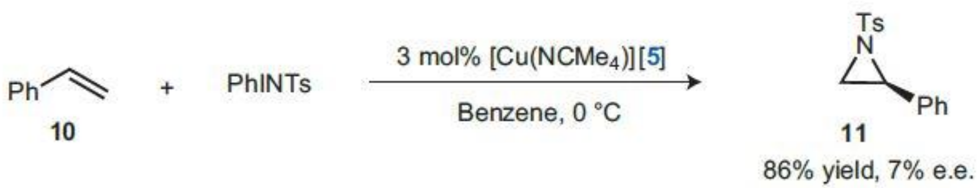
1. Introduction

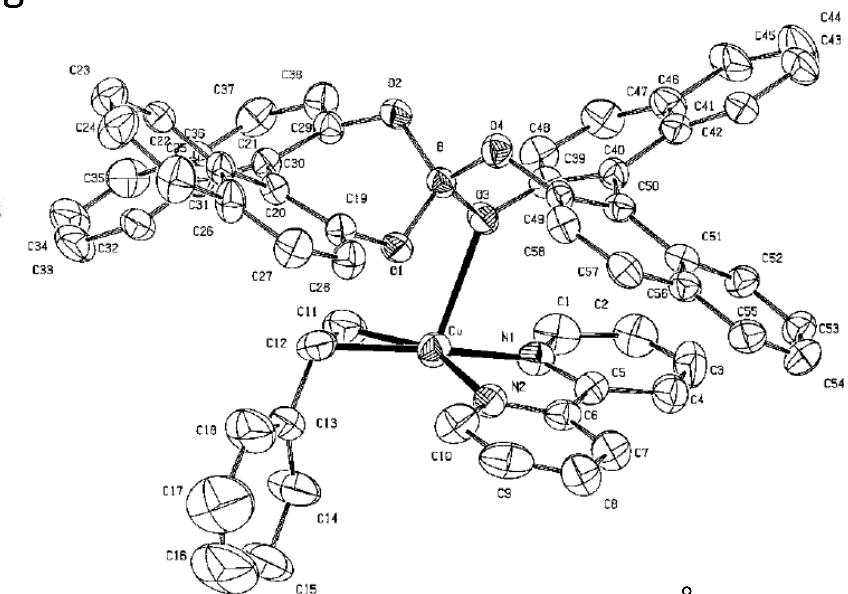
Early uses of chiral anions and their conjugate acids:

as tools for the resolution and spectroscopic analysis of chiral molecules



Intellectual foundations of chiral non-coordinating anions





Cu−O, 2.55 Å

ligand	X	% ee (C_6H_6)[b]	% ee (MeCN)[b]
(*R*)-**1**	OTf	1 (*S*)	28 (*S*)
(*R*)-**1**	ClO_4	5 (*S*)	28 (*S*)
(*R*)-**1**	Cl	17 (*S*)	28 (*S*)
(*R*)-**1**	PF_6	33 (*S*)	28 (*S*)
(*S*)-**2**	OTf	66 (*R*)	2 (*R*)
(*S*)-**2**	ClO_4	57 (*R*)	2 (*R*)
(*S*)-**2**	Cl	26 (*R*)	2 (*R*)
(*S*)-**2**	PF_6	33 (*R*)	2 (*R*)

the achiral counterion affected ee value.

Org. Lett. **2000**, 26, 4165-4168.

place the copper cation within a chiral pocket created by two separate binaphthol fragments on the boron center.

Outline:

1. Introduction

2. Applications in organocatalysis

    2.1. Chiral counterions in Brønsted acid catalysis

    2.2. Chiral counterions in Lewis acid catalysis

    2.3. Chiral counterions combining with amine

    2.4. Chiral anion binding from hydrogen-bonding catalysts

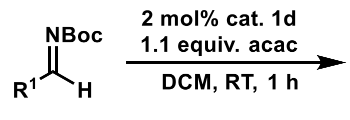
    2.5. Chiral counterions in phase-transfer catalysis

3. Conclusion

4. Acknowledgement

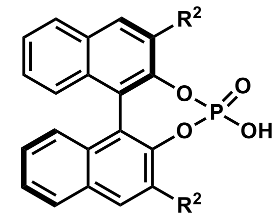
2.1. Chiral counterions in Brønsted acid catalysis

Early work using CPA by Terada (2004):



2, R^1 = subsitituted phenyl group

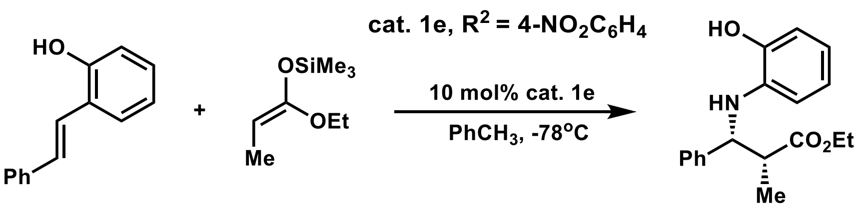
3, up to 99% yield, 99% ee, 6 examples



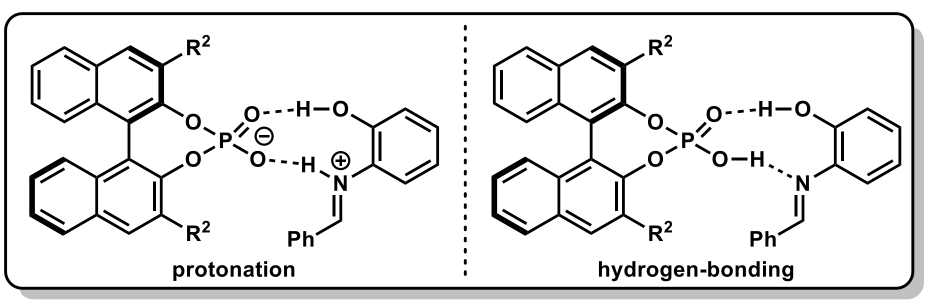
cat. 1d, R^2 = 4-(β-Naph)-C_6H_4

Brønsted acid catalysis or ion pairing?

Akiyama (2007):

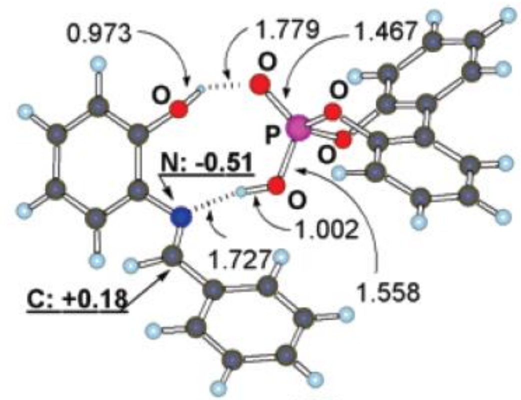


100% yield, 96% ee, 87:13 syn/anti

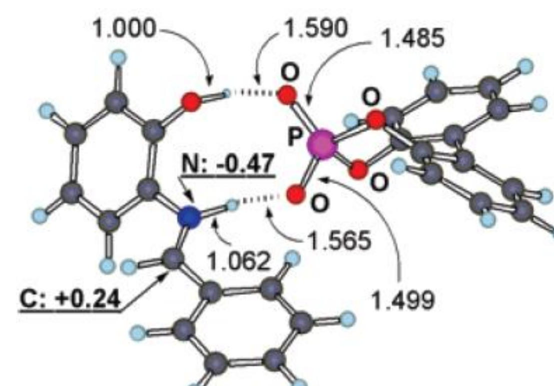


The lengths of O-H, N-H are changed dramatically through protonation.

DFT study：



CP1n

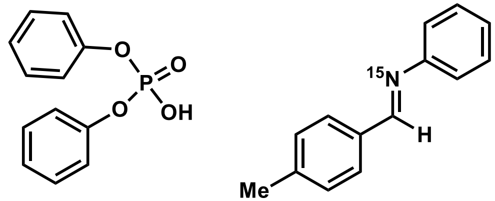


CP1i

J. Am. Chem. Soc. **2004**, 126, 5356-5357.
J. Am. Chem. Soc. **2007**, 129, 6756-6764.

2.1. Chiral counterions in Brønsted acid catalysis

NMR study :

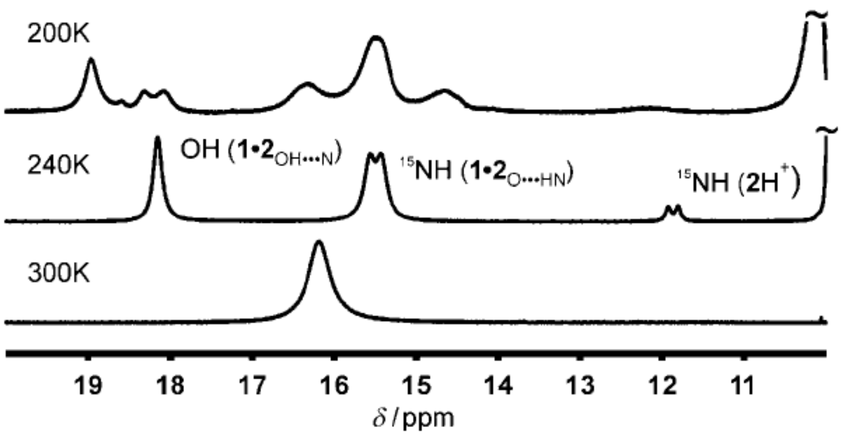


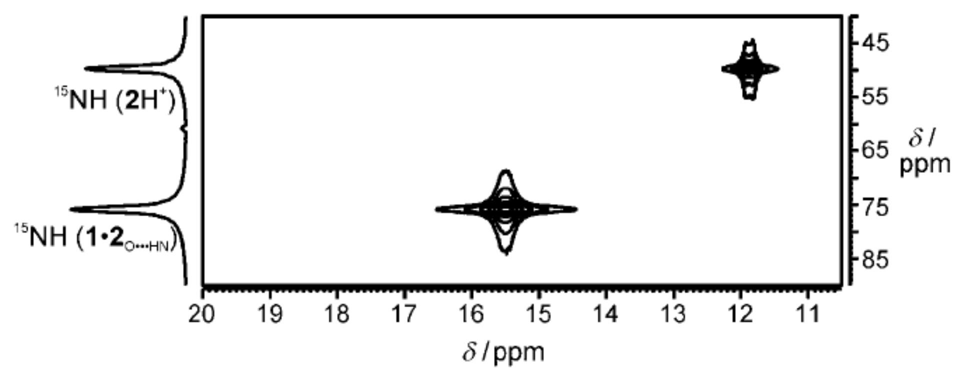
1 2

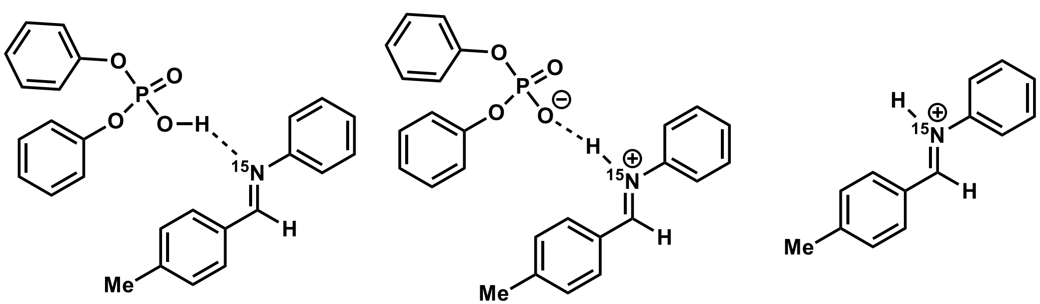
hydrogen bonds could be characterized by a combination of ^{1}H and ^{15}N NMR spectroscopy.

Possible activated modes: *(300 K = 26.8 °C; 240 K = - 33.15 °C ; 200 K = - 73.15 °C)*

2D ^{1}H,^{15}N HMQC spectrum:





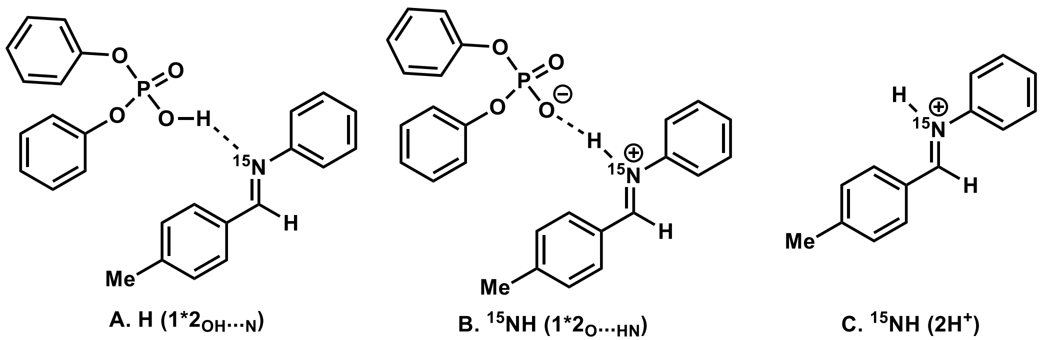


A. H ($1*2_{OH\cdots N}$) B. ^{15}NH ($1*2_{O\cdots HN}$) C. ^{15}NH ($2H^{+}$)

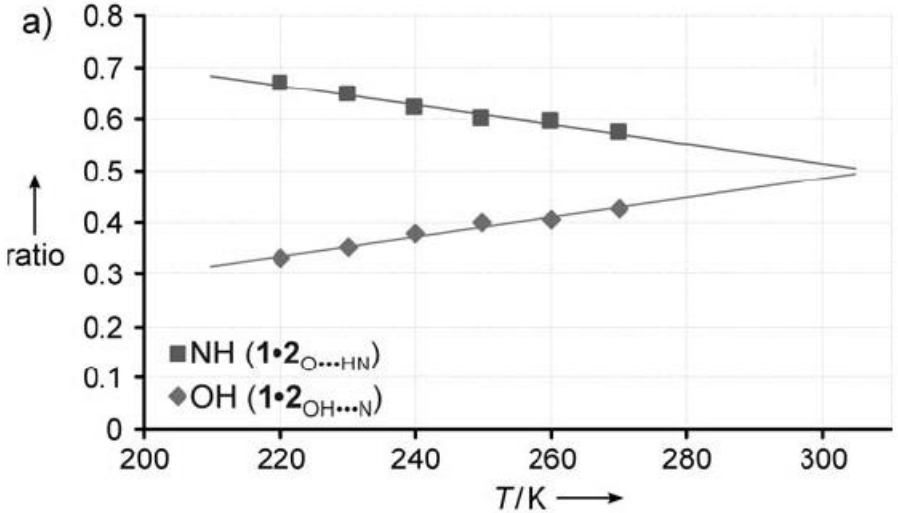
both species OH($1{\cdot}2_{OH\cdots N}$) and NH($1{\cdot}2_{O\cdots HN}$) coexist simultaneously

Angew. Chem. Int. Ed. **2011**, 50, 6364 –6369.

2.1. Chiral counterions in Brønsted acid catalysis



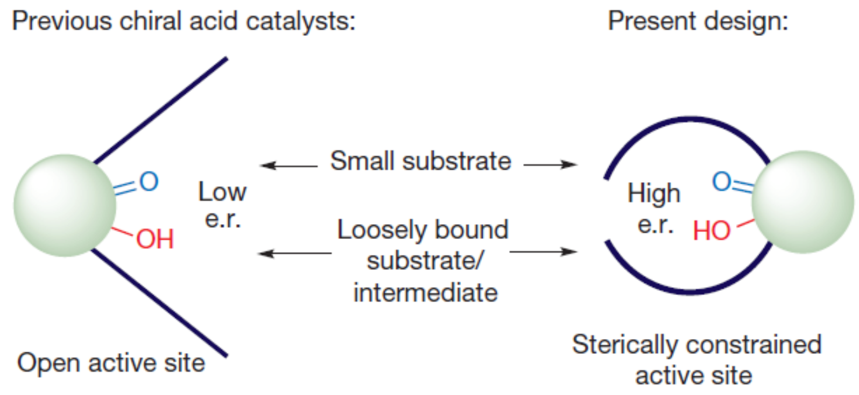
Influence of temperature:



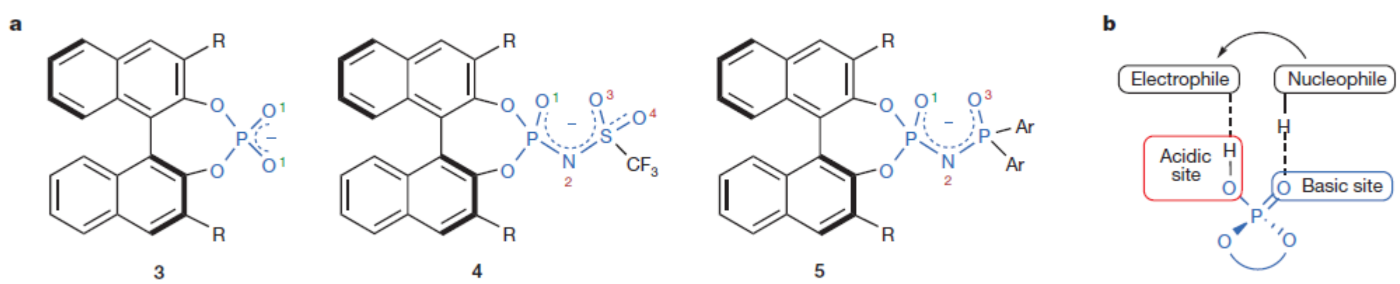
at low temperatures, the ion pairs NH($1{\cdot}2_{O\cdots HN}$) are stabilized;
at increasing temperatures, the hydrogen-bonded complexes OH($1{\cdot}2_{OH\cdots N}$) become favored.

Angew. Chem. Int. Ed. **2011**, 50, 6364 –6369.

2.1. Chiral counterions in Brønsted acid catalysis



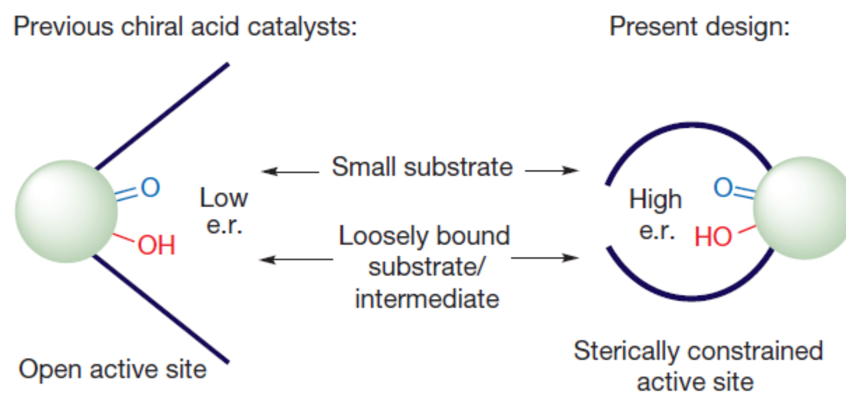
Design of new chiral Brønsted acid :



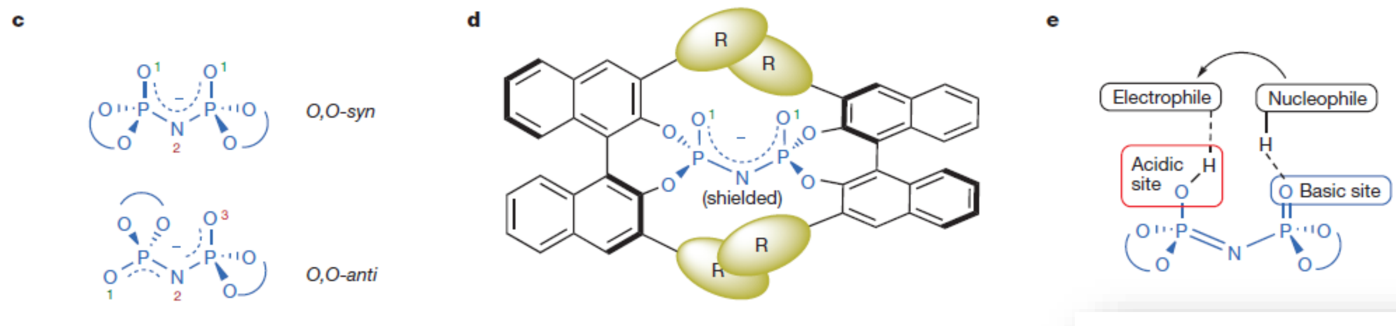
- ➡ 3,3'-substituents on BINOL radiate away from active site;
- ➡ More than one base/acid pairs in 4 and 5;
- ➡ Low selectivity

Nature **2012**, 483, 315–319.

2.1. Chiral counterions in Brønsted acid catalysis

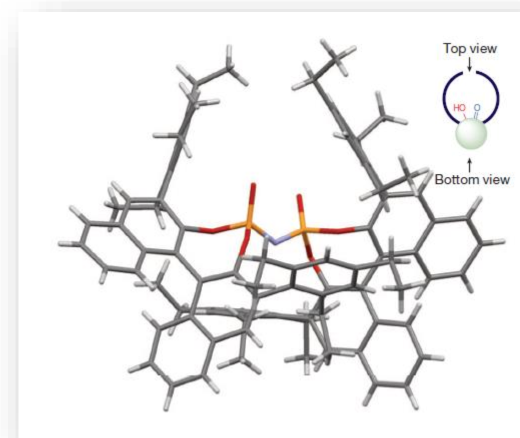


Design of new chiral Brønsted acid :



6

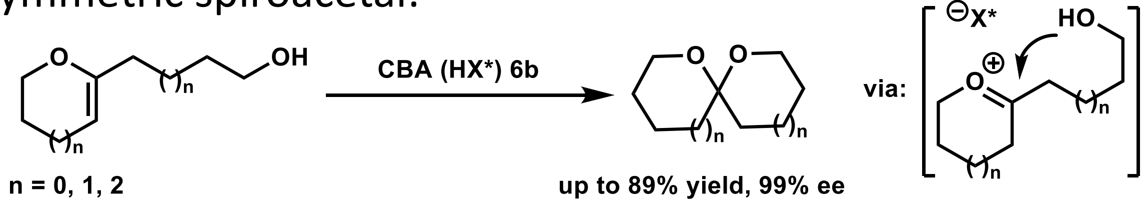
- ➡ Bulky 3,3'-substituents restrict *O,O-syn* conformation;
- ➡ High rigidity;
- ➡ Steric blocking of alternative Brønsted basic N-site;
- ➡ high selectivity



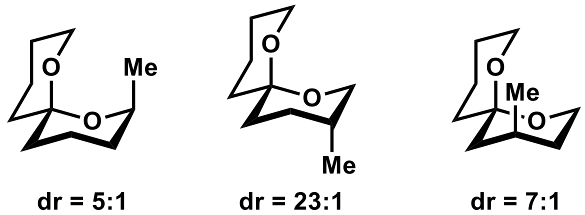
Nature **2012**, 483, 315–319.

2.1. Chiral counterions in Brønsted acid catalysis

Asymmetric spiroacetal:

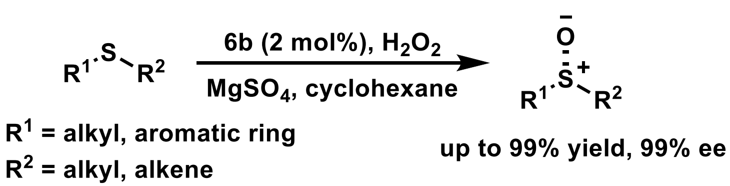


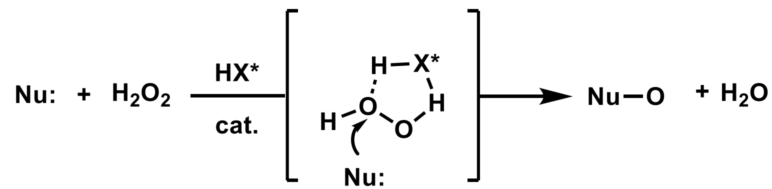
R = 2,4,6-$Me_3C_6H_2$ (**6a**)
2,4,6-$Et_3C_6H_2$ (**6b**)
9-anthracenyl (**6c**)

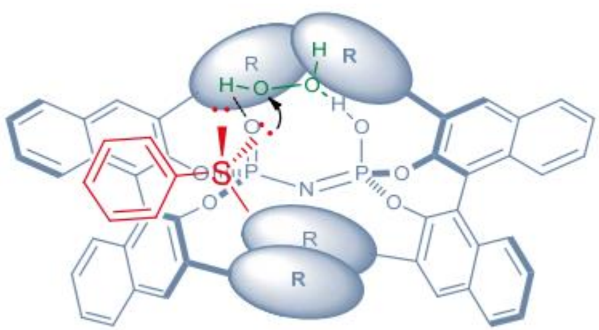


Non-thermodynamic configuration

Enantioselective Sulfoxidation:





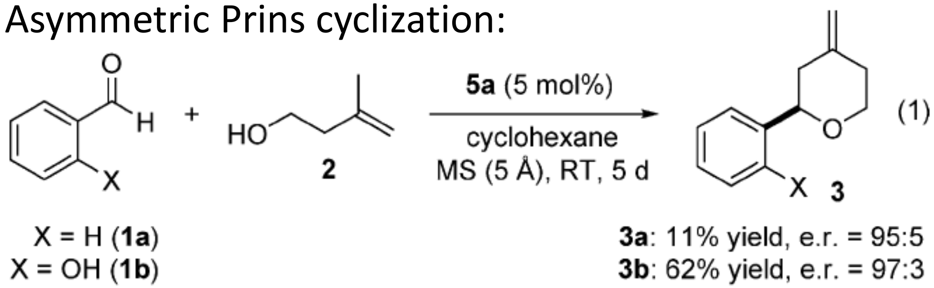


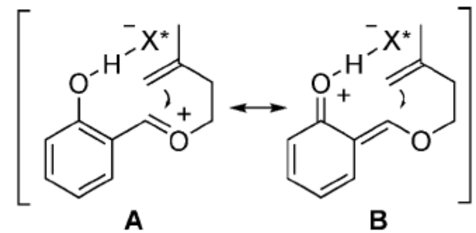
H_2O_2 could be activated in a well-defined and narrow position within a chiral cavity

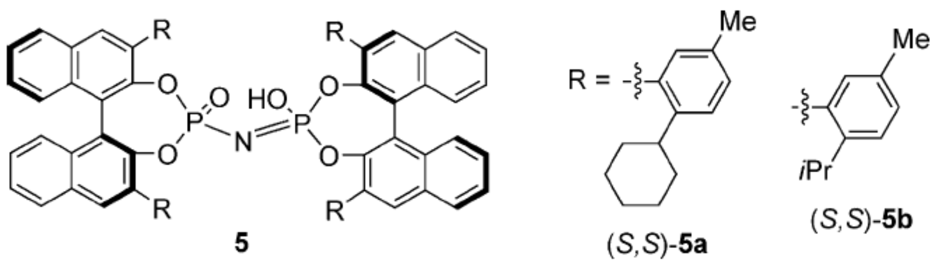
Nature **2012**, 483, 315–319.
J. Am. Chem. Soc. **2012**, 134, 10765–10768

2.1. Chiral counterions in Brønsted acid catalysis

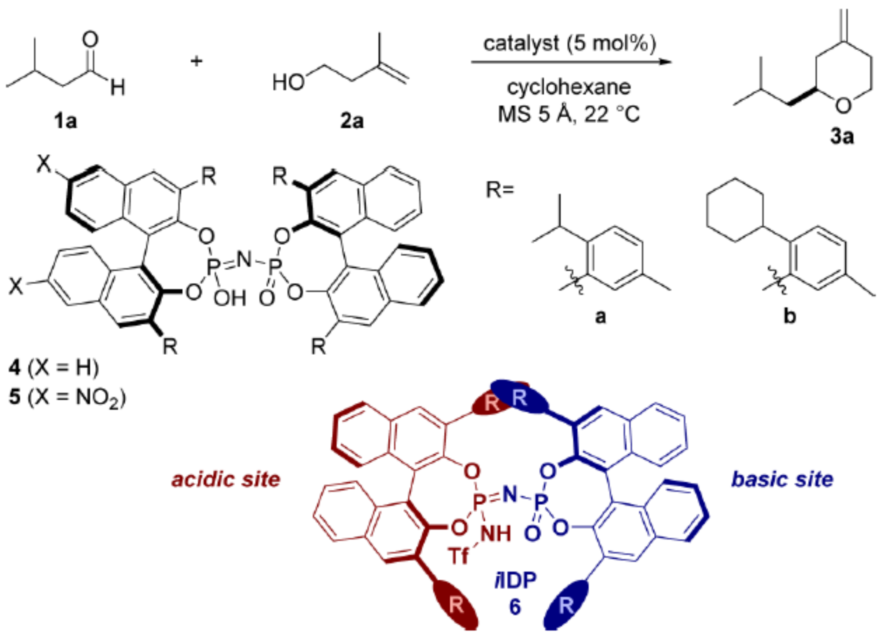
Asymmetric Prins cyclization:







Hydroxy group ortho to the aldehyde is crucial for reactivity and enantioselectivity



entry	catalyst	time (days)	conv. (3a) (%)	er[b]
1	4a	5	7	ND
2	4b	5	13	ND
3	5a	5	52	91:9
4	5b	2.5	83	87:13
5	6a	2.5	>99	95.5:4.5
6	6b	2.5	>99	94:6

➡ Electron-withdrawing nitro group

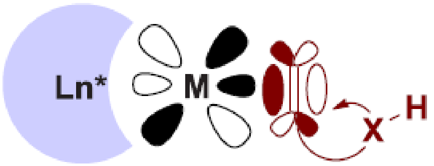
➡ Strong electron acceptor (NTf group)

High acidity

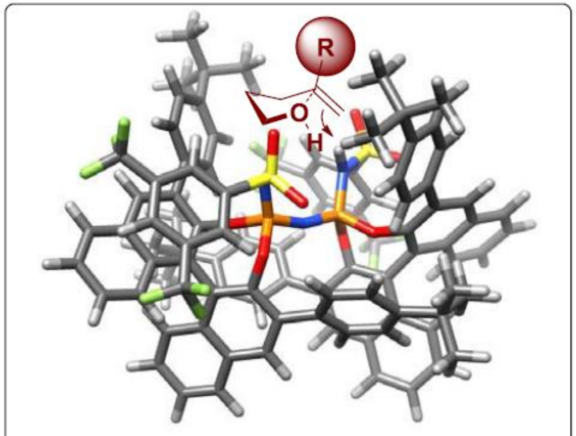
Angew. Chem. Int. Ed. **2015**, 54, 7703 –7706;
J. Am. Chem. Soc. **2016**, 138, 10822–10825

2.1. Chiral counterions in Brønsted acid catalysis

Asymmetric reaction of olefins relies on transitional metal catalysis:

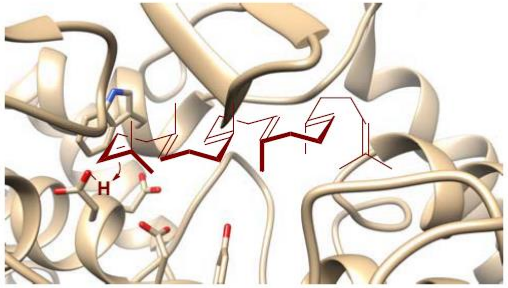


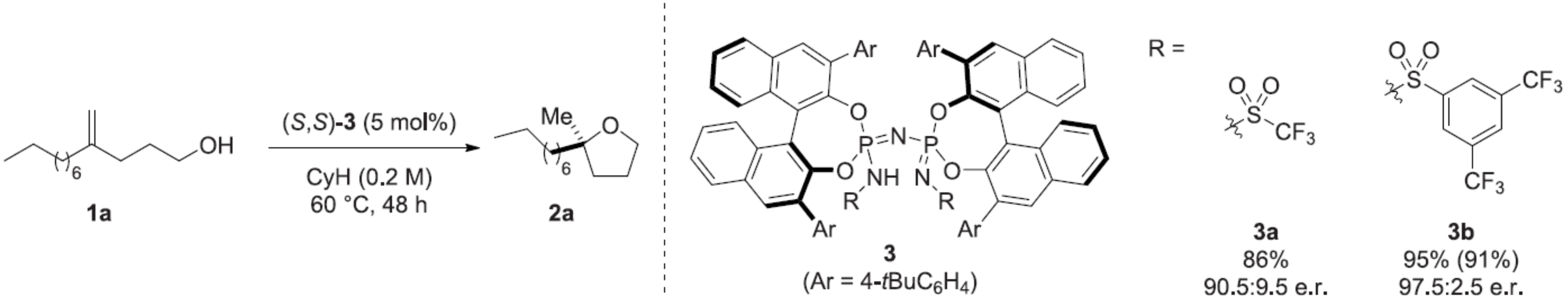
Activation of olefins via ACDC:



***Organocatalysis* (3b)**

- ➡ high acidity to enable olefin protonation
- ➡ a confined, enzyme-like microenvironment to favor the desired transformation with high selectivity

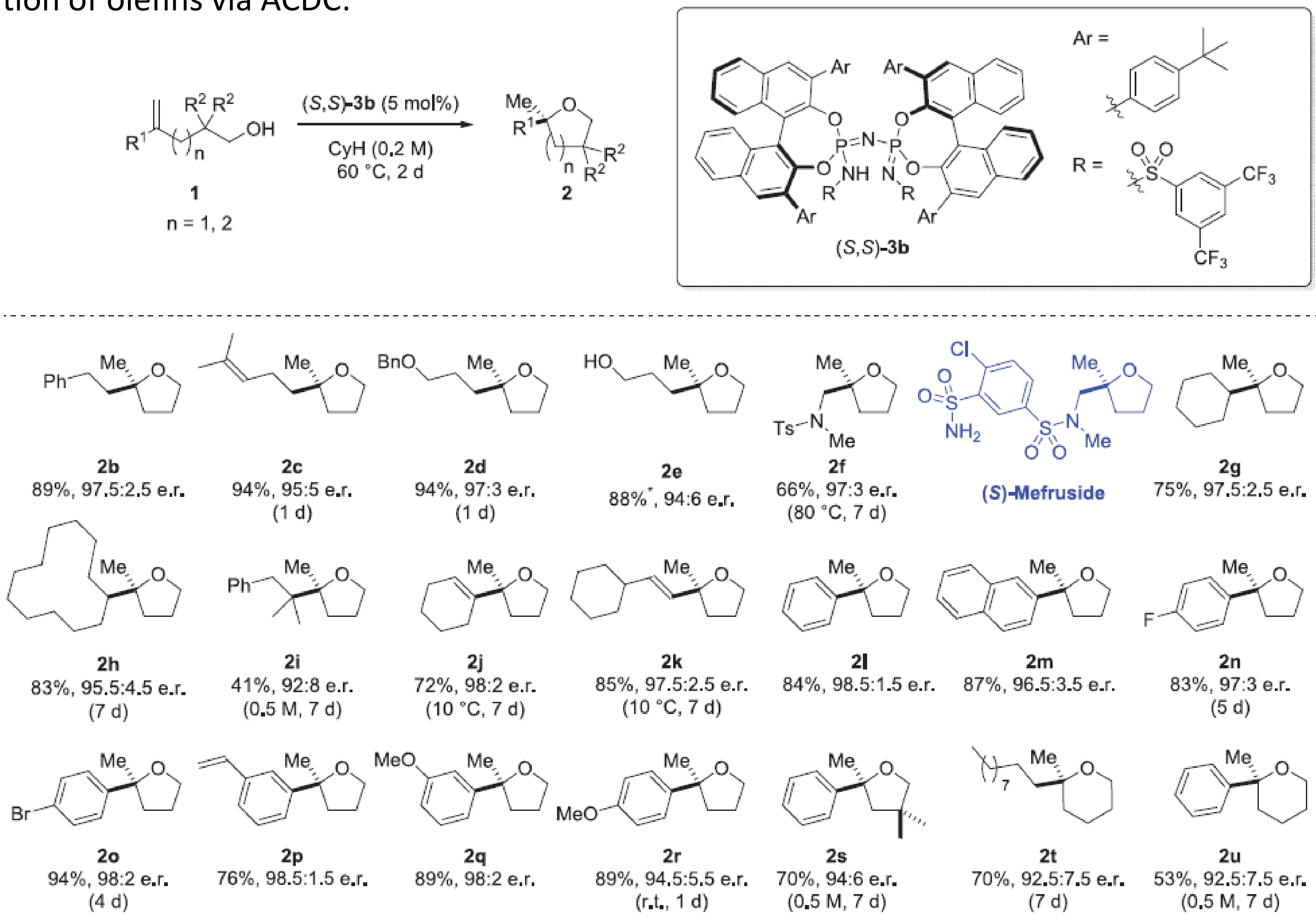




Science **2018**, 359, 1501–1505.

2.1. Chiral counterions in Brønsted acid catalysis

Activation of olefins via ACDC:

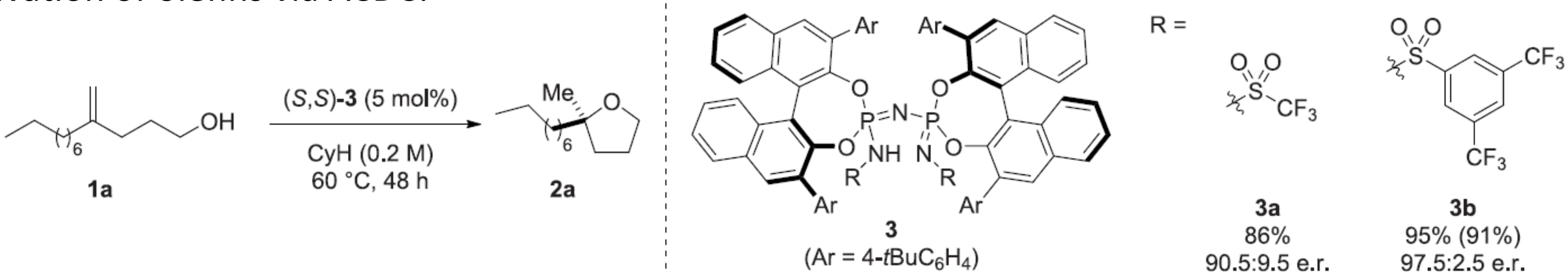


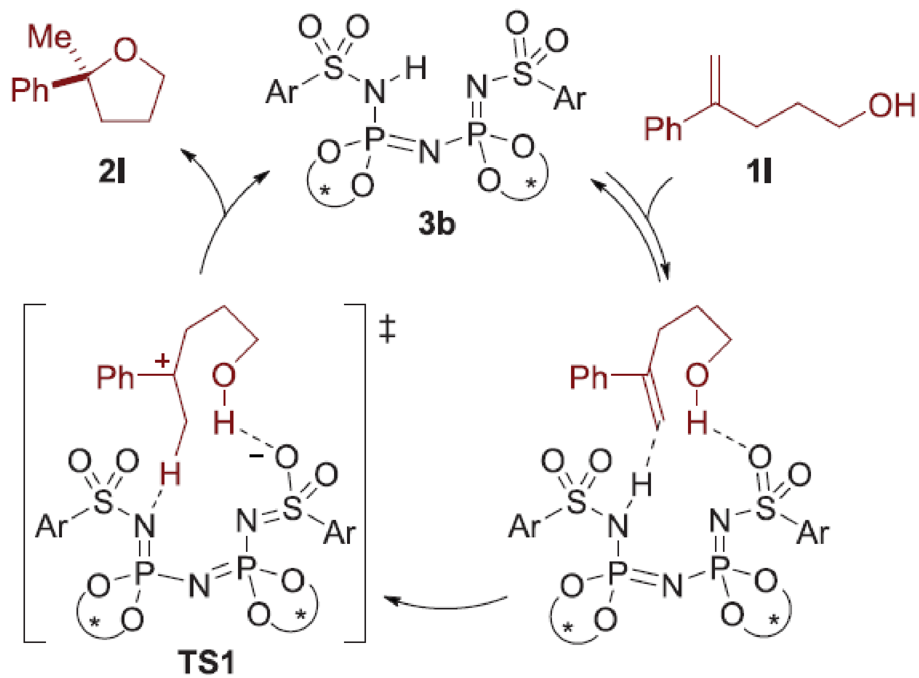
Only 1,1'-disubtituted alkenes worked in this reaction conditions.

Science **2018**, 359, 1501–1505.

2.1. Chiral counterions in Brønsted acid catalysis

Activation of olefins via ACDC:





Through DFT, The lowest energy transition state TS1 suggests a concerted though asynchronous mechanism.

Science **2018**, 359, 1501–1505.

Outline:

1. Introduction

2. Applications in organocatalysis

   2.1. Chiral counterions in Brønsted acid catalysis

   2.2. Chiral counterions in Lewis acid catalysis

   2.3. Chiral counterions combining with amine

   2.4. Chiral anion binding from hydrogen-bonding catalysts

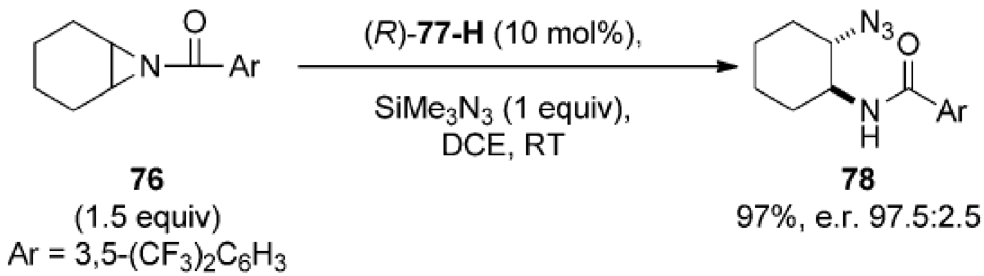
   2.5. Chiral counterions in phase-transfer catalysis

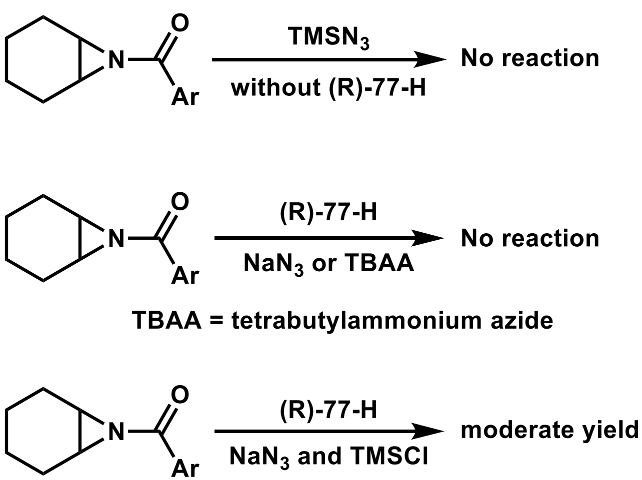
3. Conclusion

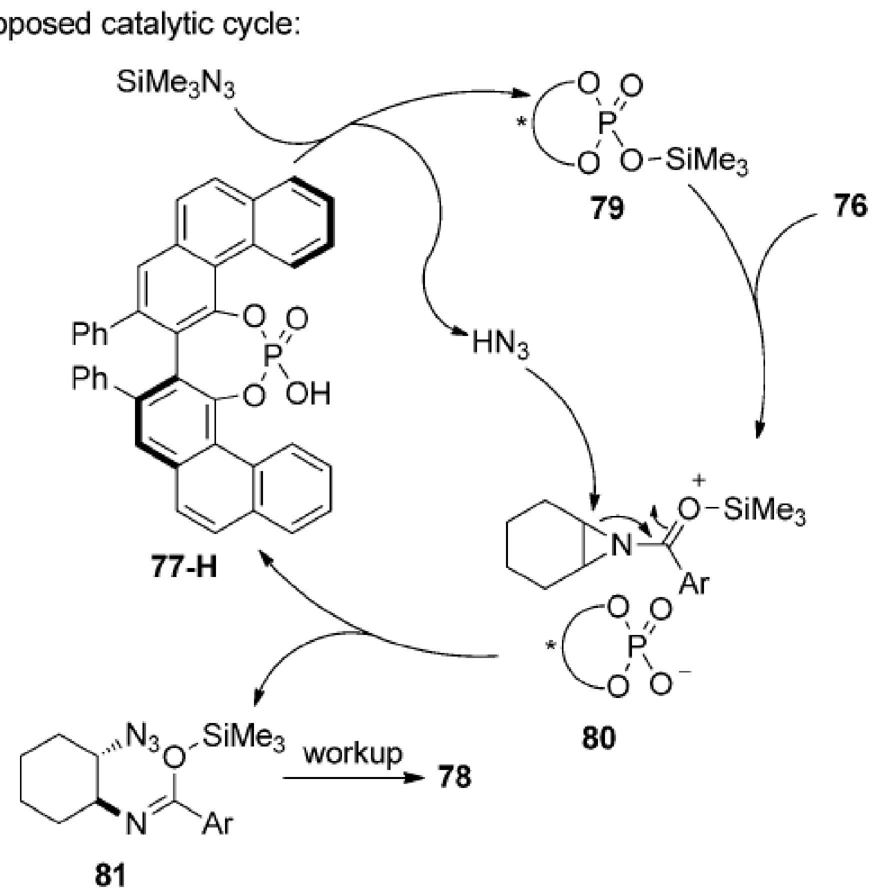
4. Acknowledgement

2.2. Chiral counterions in Lewis acid catalysis

The first example of asymmetric counteranion-directed Lewis acid catalysis:





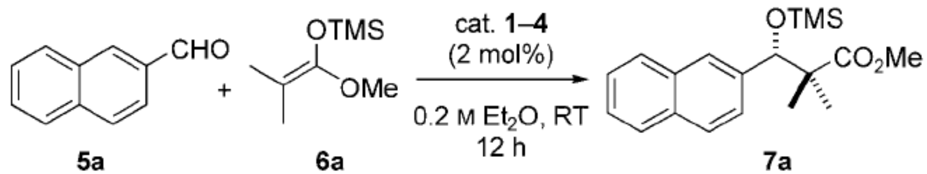


Chiral silane was generated in situ as active catalyst

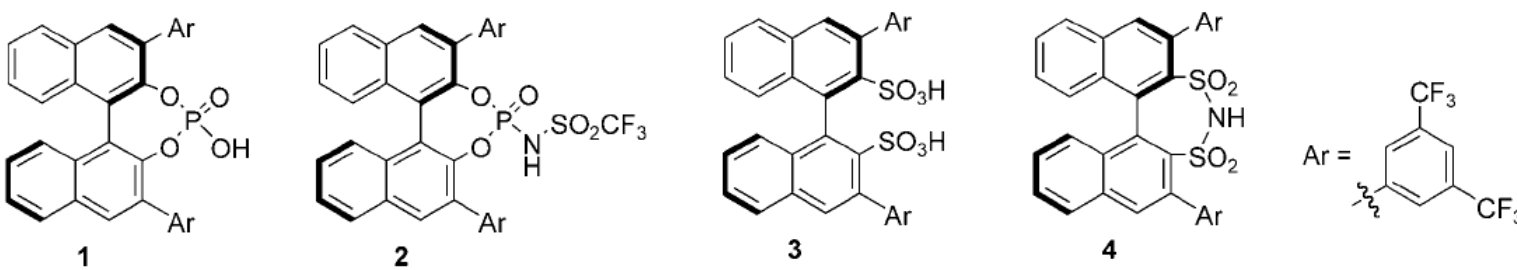
J. Am. Chem. Soc. **2007**, 129, 12084-12085

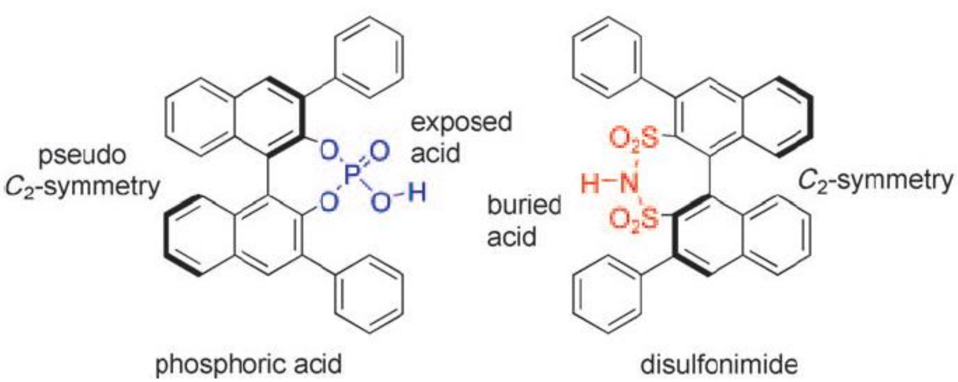
2.2. Chiral counterions in Lewis acid catalysis

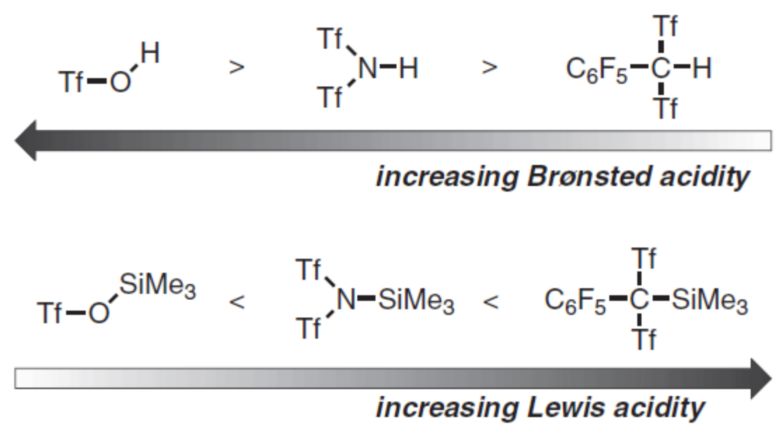
Enantioselective Mukaiyama aldol reaction:



Entry	Catalyst	Yield [%][a]	e.r.[b,c]
1	**1**	< 2	–
2	**2**	< 2	–
3	**3**	< 2	–
4	**4**	> 99	90:10





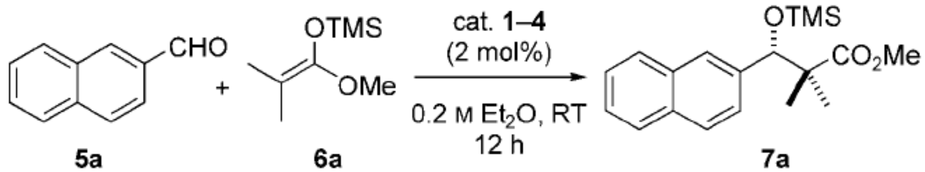


stronger Lewis acid worked better.

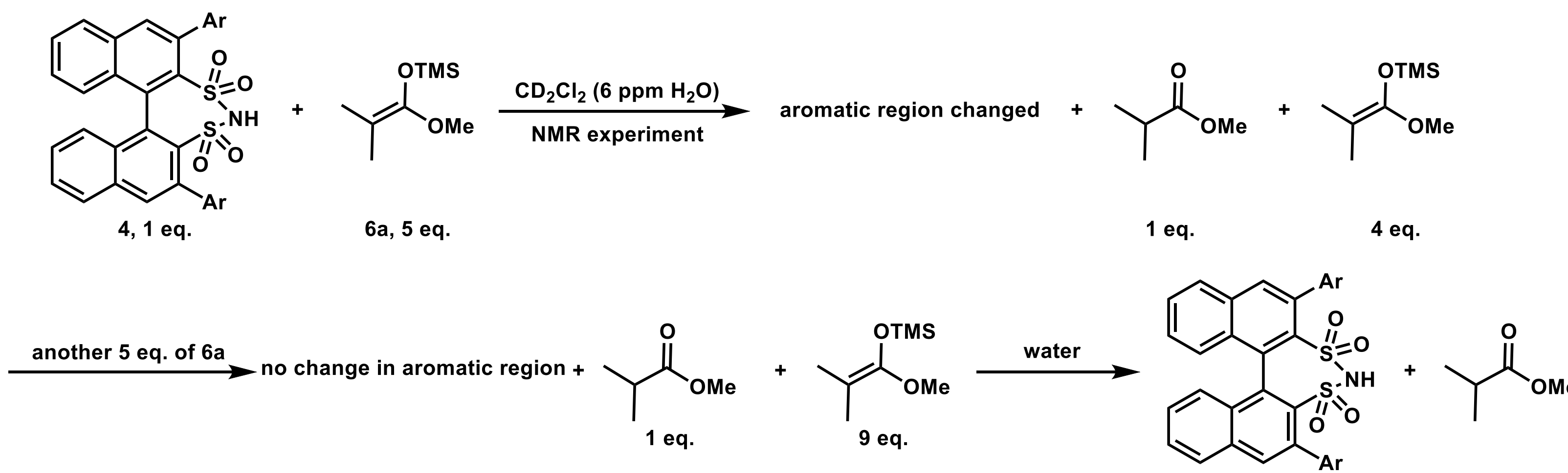
Angew. Chem. Int. Ed. **2009**, 48, 4363–4366

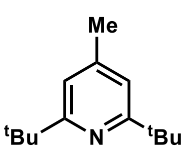
2.2. Chiral counterions in Lewis acid catalysis

Enantioselective Mukaiyama aldol reaction:



Mechanism study:

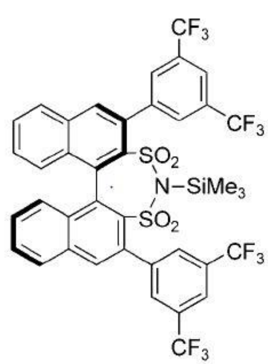




base (inhibit any potential CBA catalysis)

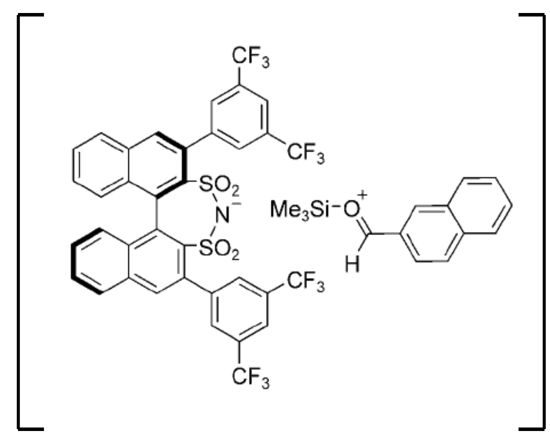
1.2 eq in standard reaction, full conversion of product

Angew. Chem. Int. Ed. **2009**, 48, 4363–4366

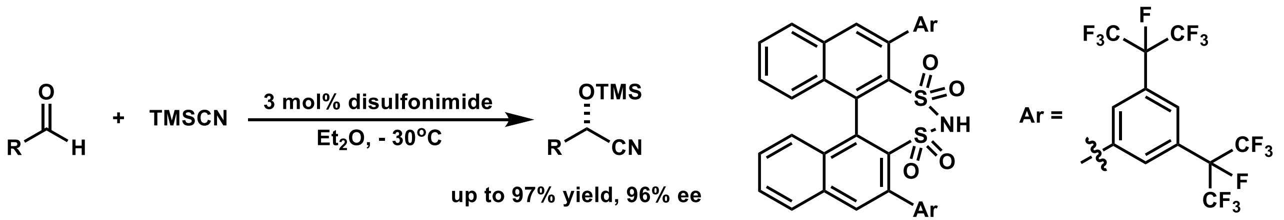


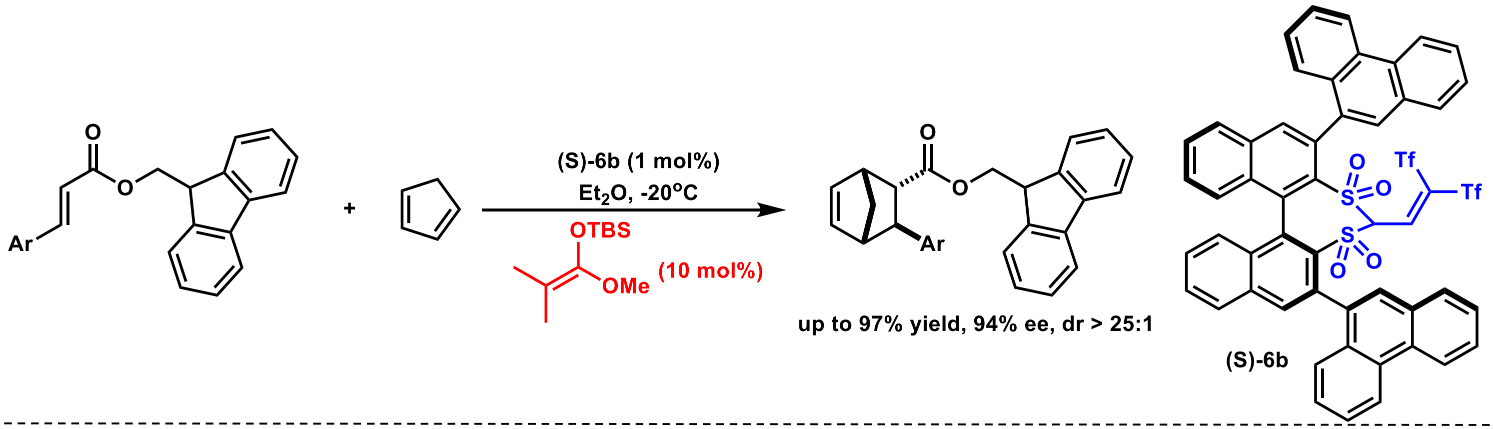
active catalyst generated in situ

via:



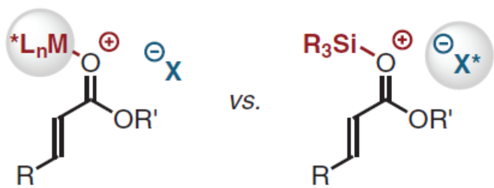
2.2. Chiral counterions in Lewis acid catalysis





Conventional approaches to enantioselective Lewis acid catalysis:

- chirality directly attached to Lewis acid
- complexation between chiral catalyst and substrate
- achiral counteranion present, if Lewis acid is cationic



Asymmetric counteranion-directed catalysis with catalytic silylium ion equivalents (silylium ion–ACDC):

- chirality at the counteranion
- Coulomb interaction between chiral anion and activated substrate
- silylium ion equivalent = highly active Lewis acid catalyst

Nature communication. **2016**, 7, 12478.
Science, **2016**, 351, 949.

Outline:

1. Introduction

2. Applications in organocatalysis

    2.1. Chiral counterions in Brønsted acid catalysis

    2.2. Chiral counterions in Lewis acid catalysis

    2.3. Chiral counterions combining with amine

    2.4. Chiral anion binding from hydrogen-bonding catalysts

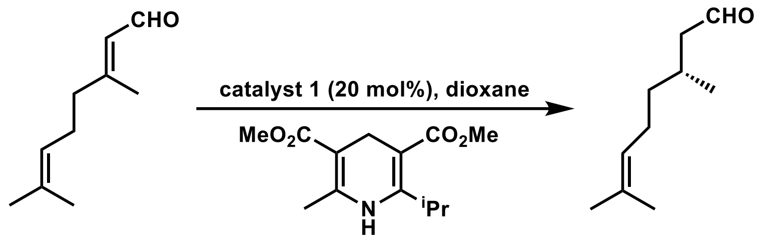
    2.5. Chiral counterions in phase-transfer catalysis

3. Conclusion

4. Acknowledgement

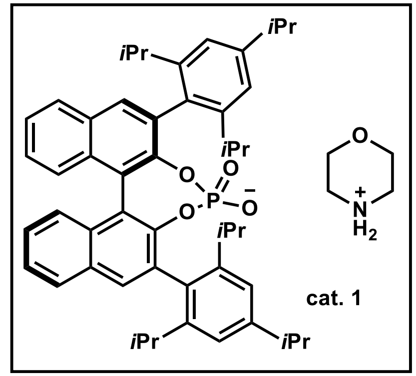
2.3. Chiral counterions combining with amine

Secondary amine:

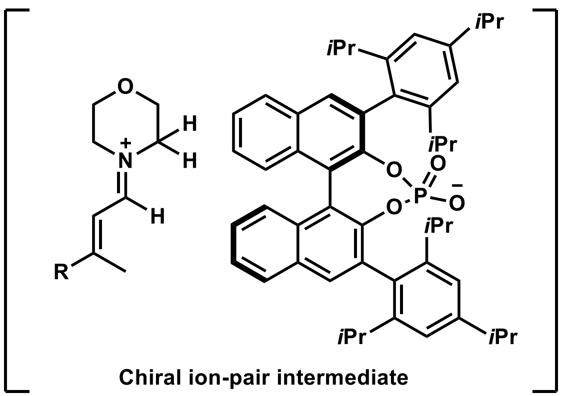


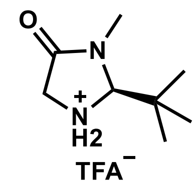
(E)-citral

71% yield, 90% ee

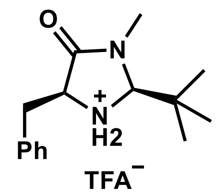


via:

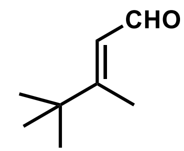




58% yield, 40% ee

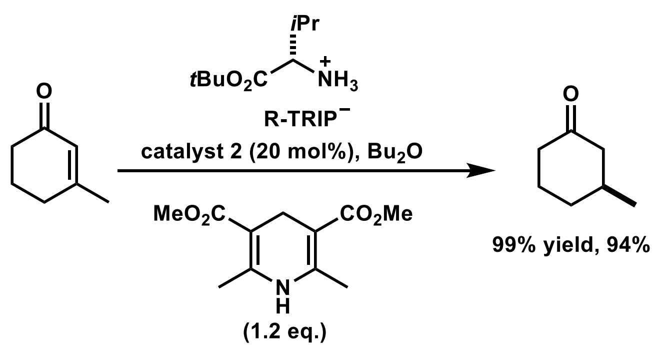


82% yield, 40% ee



hindered aliphatic substrate 2g
< 5% yield, no ee

Primary amine:

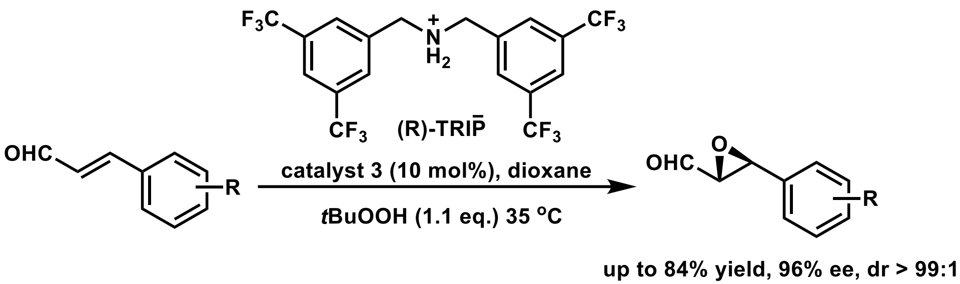


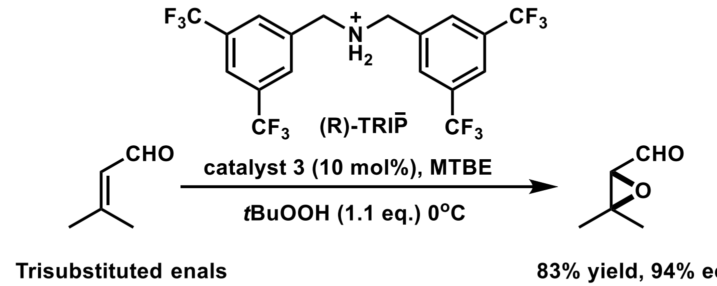
99% yield, 94% ee

Angew. Chem. Int. Ed. **2006**, 45, 4193–4195.
J. Am. Chem. Soc. **2006**, 128, 13368-13369.

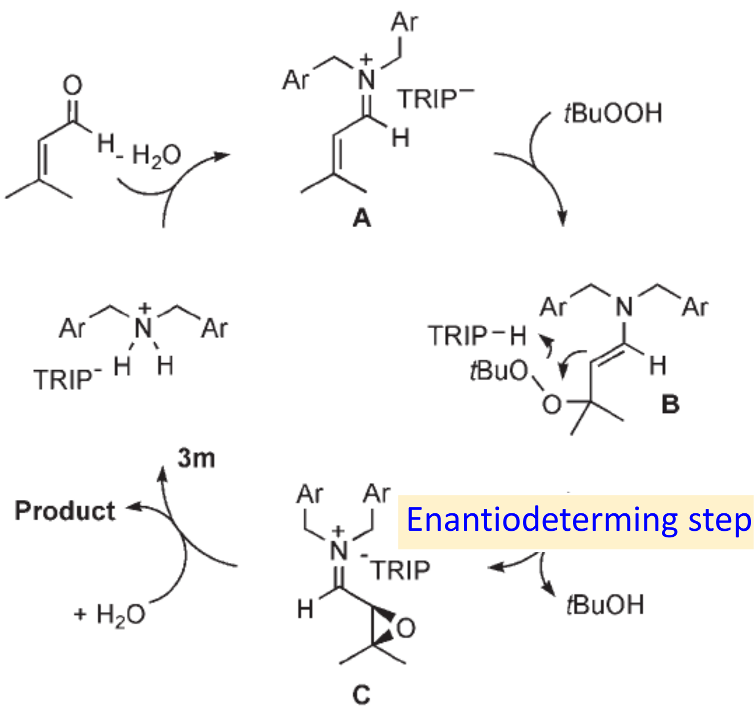
2.3. Chiral counterions combining with amine

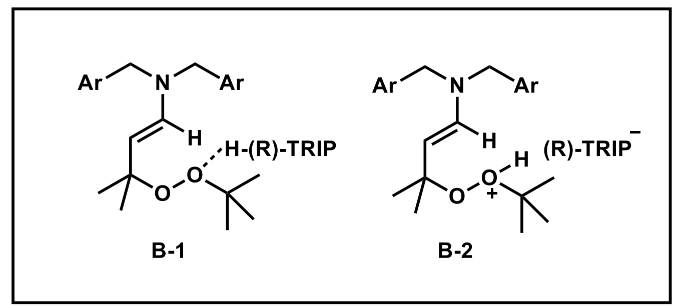
Enantioselective epoxidation of enals:





Proposed catalytic cycle:





The primary product of the cyclization, C, is a chiral iminium–TRIP ion pair. This indicates that the transition state leading to C will also have ion-pair character.

Angew. Chem. Int. Ed. **2008**, 47, 1119 –1122.

Outline:

1. Introduction

2. Applications in organocatalysis

    2.1. Chiral counterions in Brønsted acid catalysis

    2.2. Chiral counterions in Lewis acid catalysis

    2.3. Chiral counterions combining with amine

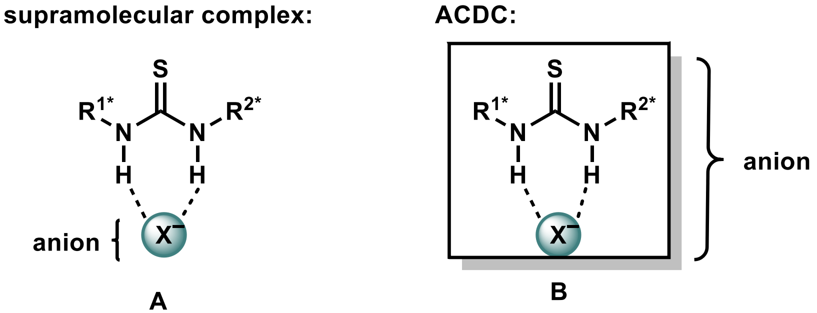
    2.4. Chiral anion binding from hydrogen-bonding catalysts

    2.5. Chiral counterions in phase-transfer catalysis

3. Conclusion

4. Acknowledgement

2.4. Chiral anion binding from hydrogen-bonding catalysts

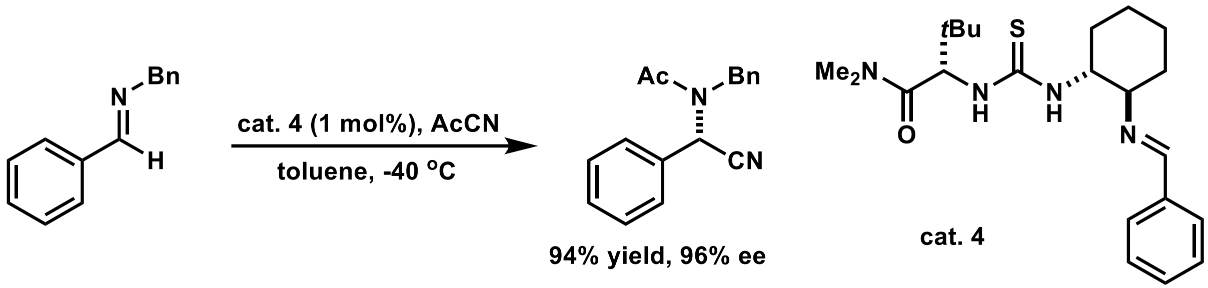


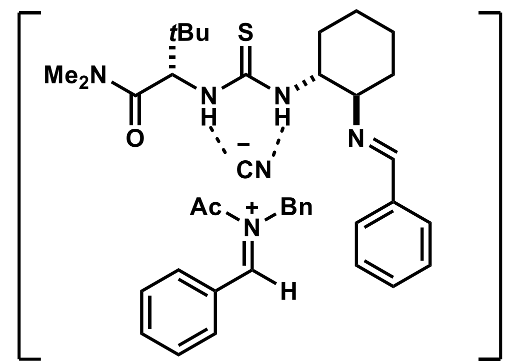
A: anion remains achiral

B: the complex of thiourea and the leaving group can be considered to be anionic part

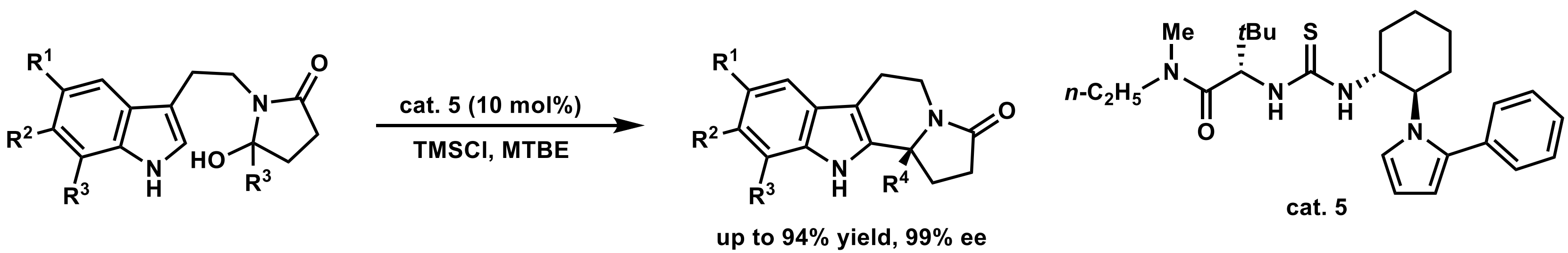
---

Acylcyanation of imines:





Pictet-Spengler-Type Cyclizations of hydroxylactams:



Angew. Chem. Int. Ed. **2007**, 46, 612 –614.
J. Am. Chem. Soc. **2007**, 129, 13404-13405.

Outline:

1. Introduction

2. Applications in organocatalysis

    2.1. Chiral counterions in Brønsted acid catalysis

    2.2. Chiral counterions in Lewis acid catalysis

    2.3. Chiral counterions combining with amine

    2.4. Chiral anion binding from hydrogen-bonding catalysts

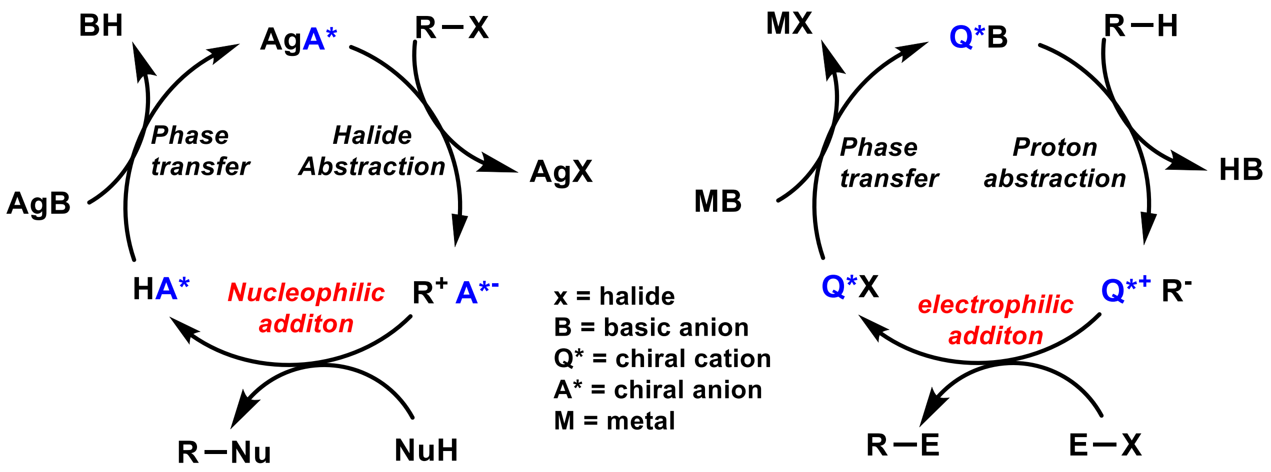
    2.5. Chiral counterions in phase-transfer catalysis

3. Conclusion

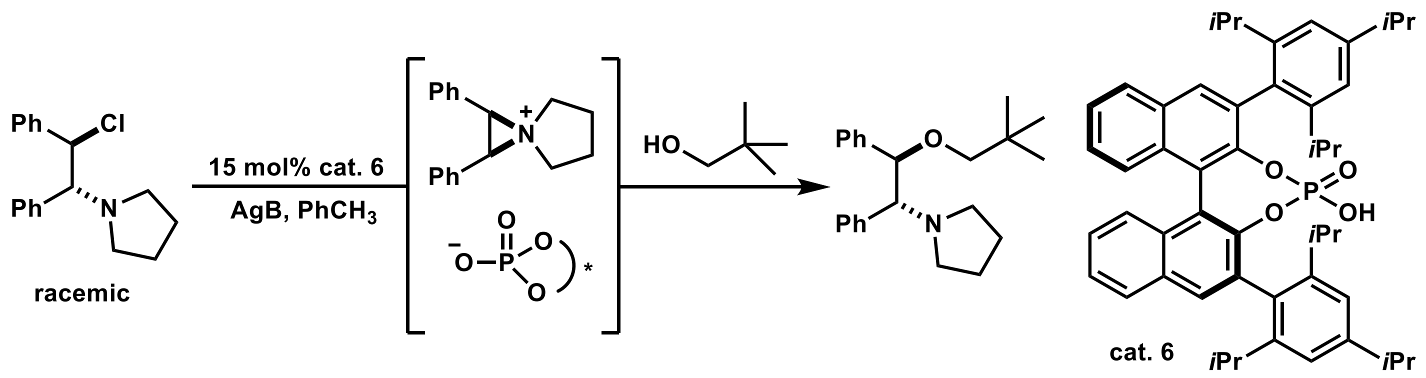
4. Acknowledgement

2.5. Chiral counterions in phase-transfer catalysis

Chiral anion phase transfer catalysis compared to chiral cation PTC:



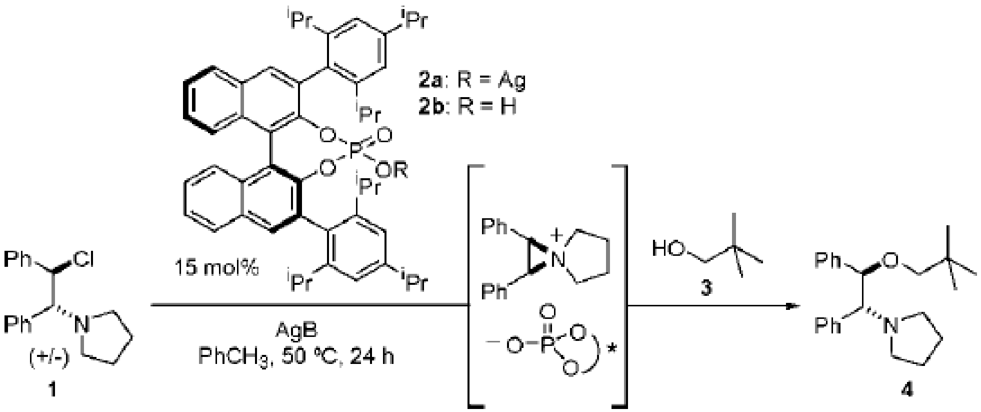
Asymmetric ring opening with anionic chiral PTC:



J. Am. Chem. Soc. **2008**, 130, 14984–14986.

2.5. Chiral counterions in phase-transfer catalysis

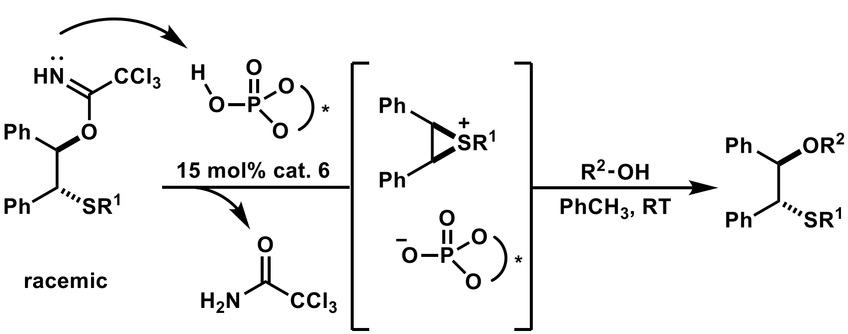
Asymmetric ring opening with anionic chiral PTC:



The failure of Ag_2CO_3 to promote the reaction alone is consistent with PTC role of the phosphrate anion.

entry	catalyst	AgB	additive	yield (%)[a]	ee (%)[b]
1	**2a**	Ag_2CO_3	none	77	94
2	**2a**	AgOTs	none	88	56
3	**2b**	Ag_2CO_3	none	74	94
4	**2b**	none	none	trace	ND
5	none	Ag_2CO_3	none	trace	ND
6	**2b**	Ag_2CO_3	4Å ms	84	94
7	**2b** (recycled)	Ag_2CO_3	4Å ms	83	94

Addition of more soluble silver compounds such as AgOTs led to significantly lower ee due to competition from the achiral anion

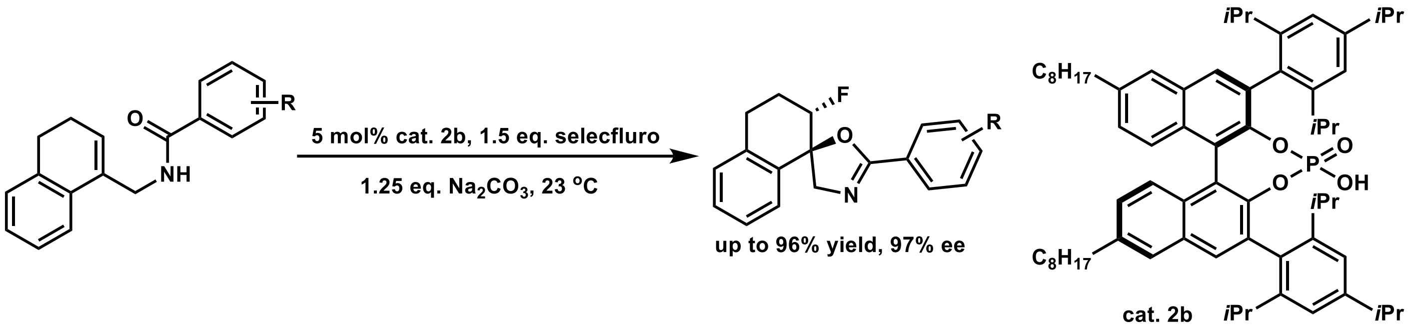


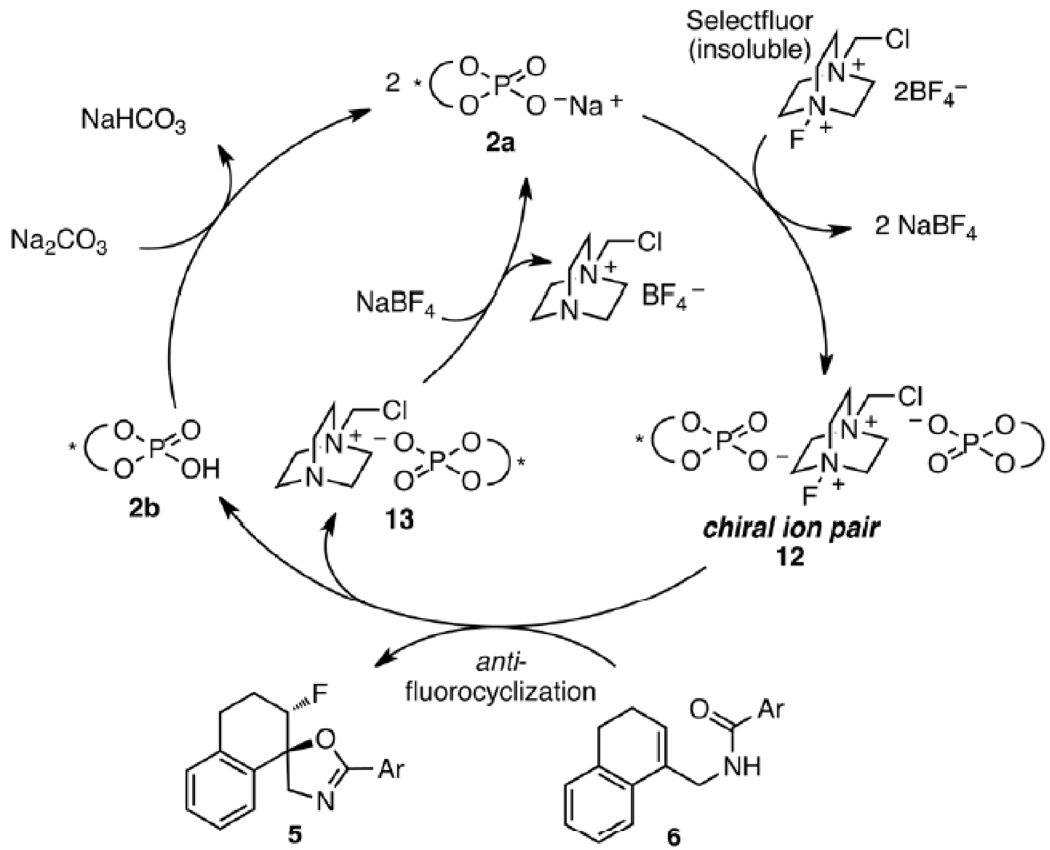
Trichloroacetimidate as leaving group

J. Am. Chem. Soc. **2008**, *130*, 14984–14986.

2.5. Chiral counterions in phase-transfer catalysis

Asymmetric electrophilic fluorination with anionic chiral PTC:

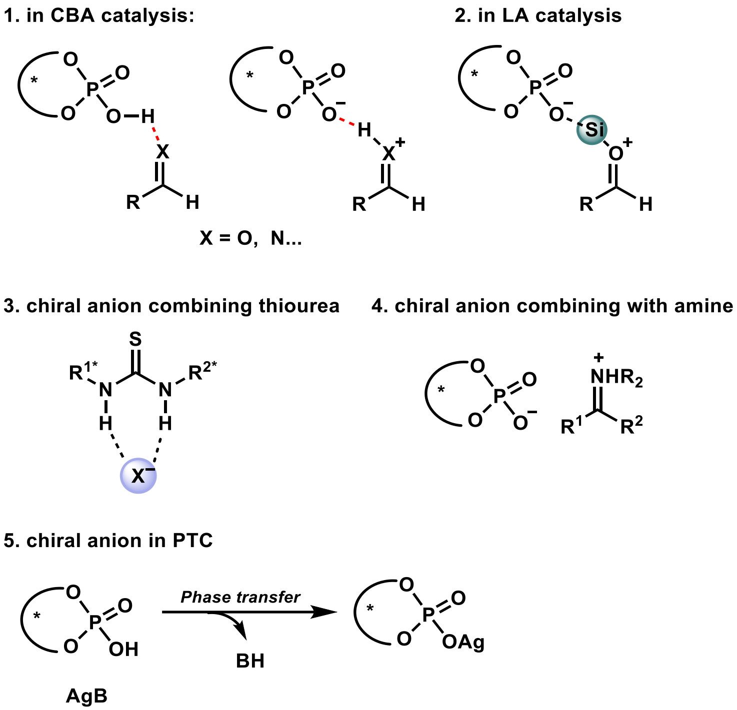




science **2011**, 334, 1681–1684.

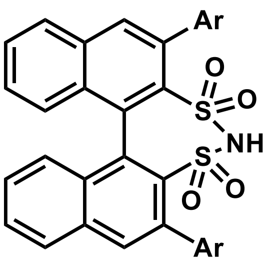
4. Conclusion

➡ *Five reaction modes of chiral anion: realization of asymmetric reaction in good selectivty*



➡ *Most substrates restricted to aldehyde or ketones in CBA and LA catalysis*

➡ *Application in photocatalysis, activation of alkene or alkyne*



buried acid with big subtituents

Acknowledgement

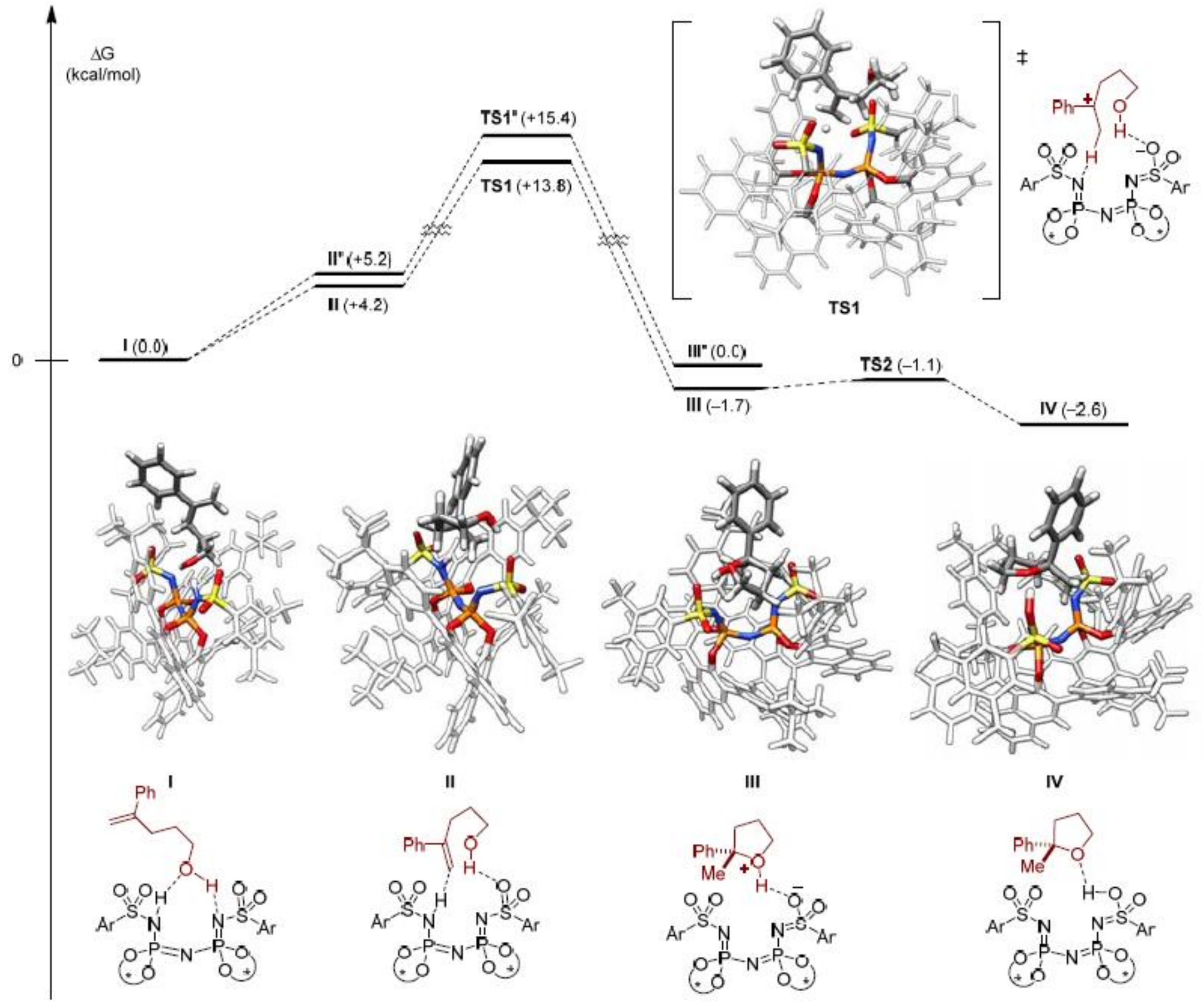
Prof. Huang

Dr. Chen

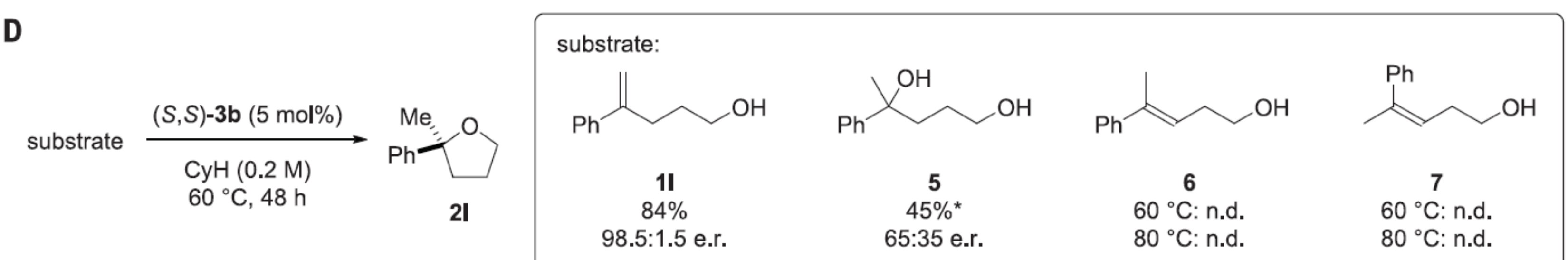
All members in E201

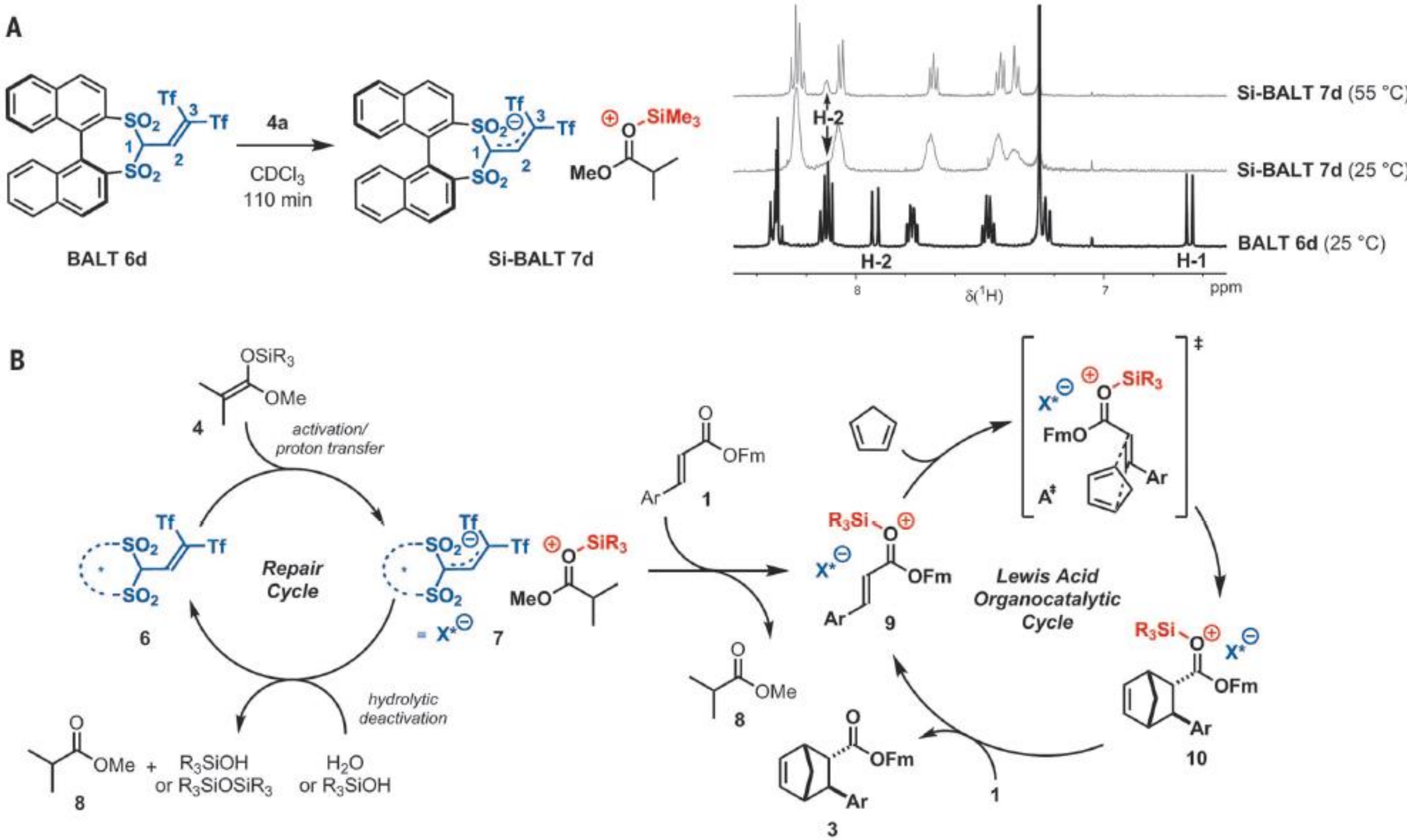
Everyone here

Thank you!


ΔG
(kcal/mol)
0
I (0.0)
II' (+5.2)
II (+4.2)
TS1' (+15.4)
TS1 (+13.8)
III' (0.0)
III (–1.7)
TS2 (–1.1)
IV (–2.6)
‡
TS1
I
II
III
IV
Ph
Ar

D


substrate
(S,S)-3b (5 mol%)
CyH (0.2 M)
60 °C, 48 h
Me
Ph
O
2l
substrate:
Ph
OH
1l
84%
98.5:1.5 e.r.
5
45%*
65:35 e.r.
6
60 °C: n.d.
80 °C: n.d.
7
60 °C: n.d.
80 °C: n.d.


A
BALT 6d
4a
CDCl3
110 min
Si-BALT 7d
Tf
Tf
SO2
SO2
MeO
SiMe3
H-2
H-1
Si-BALT 7d (55 °C)
Si-BALT 7d (25 °C)
BALT 6d (25 °C)
δ(1H)
ppm
B
OSiR3
OMe
4
activation/
proton transfer
Repair
Cycle
6
7
= X*
SiR3
hydrolytic
deactivation
OMe
8
R3SiOH
or R3SiOSiR3
H2O
or R3SiOH
Ar
1
OFm
R3Si
X*
9
Lewis Acid
Organocatalytic
Cycle
FmO
A‡
10
3